Mitochondrial DNA Mutations as Biomarkers of Early Cancer Detection

NIST, with the support of the Early Detection Research Network of the National Cancer Institute, conducted a study to resolve problems associated with the inaccuracy of published DNA sequences of the human mitochondrial genome, an important cancer diagnostic resource. Because of the potential importance of mitochondrial DNA (mtDNA) to diagnostics and forensics, it is critical that reference sequence data be of the highest integrity. mtDNA was systematically sequenced and mutations were annotated and cataloged. The work is in support of laboratory and discovery work being conducted by academia and the medical diagnosticindustry.

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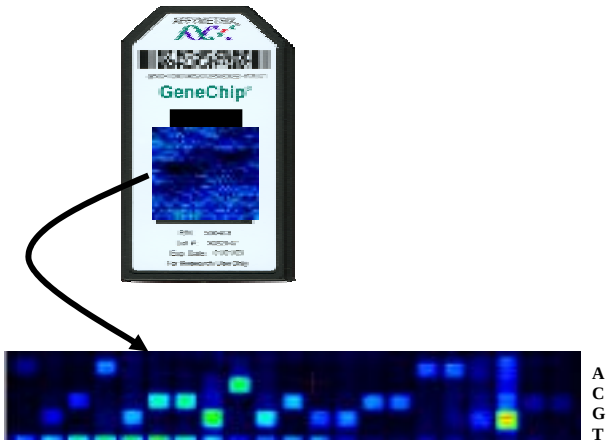
Mutations in the mitochondrial DNA (mtDNA) have been detected in colorectal, breast, cervical, ovarian, prostate, liver, pancreatic, and lung cancers. Mitochondrial dysfunction is causally related to neoplastic transformation via mutations that retard electron flow resulting in increased reactive oxygen species (ROS) production. In addition to cancer, the biological effects of mtDNA instability have been reported in degenerative diseases, neurodegenerative diseases, macular degeneration, aging and longevity and cardiovascular disease.

The utility of mtDNA mutations as biomarkers for cancer detection in tumors and non-invasively collected bodily fluids has remained poorly validated. Further, recent publications estimate that more than half of mtDNA sequence publications contain errors. A few studies using bodily fluids have been conducted, but have subsequently been shown to contain errors based on the comparison of reported sequences with databases that make up global mtDNA phylogeny. This study is therefore timely, and demonstrates that mtDNA can serve as a sensitive biomarker for cancer.

NIST is developing human mtDNA mutation reference data for use in assays to identify critical alterations in the genetic information found in the mitochondria of cancer cells. The NIST work is expected to result in new medical diagnostic innovations.

To identify mtDNA mutations in a systematic manner, the mitochondrial genome was sequenced using the MitoChip microarray, which is faster, less expensive and more sensitive than the CE DNA sequencing reference method. This work was supported in part by the Early Detection Research Network (EDRN) of the National Cancer Institute and in close collaboration with NCI's Biomarkers Research Group.



Scans entire mitochondrial genome

Optimized Resequencing Microrray to detect DNA mutations in early stage cancers (figure provided by Dr. Sidransky, NIH).

These findings indicate comprehensive mtDNA sequencing can be a high-throughput tool for detecting mutations in clinical samples and has direct application for cancer detection. This entire mitochondrial DNA analysis provides a genome wide view of the cancer associated mutations in bodily fluids. Detection and monitoring of the tumor and its field via mtDNA mutation analysis could be a practical way to assess remote sites. Our results reinforce the ideas that mtDNA mutations occur frequently in the coding region and pending the development of a mitochondrial expression array, alter (genetically) important OXPHOS genes. We envision conducting epidemiological studies of the mitochondrial genome to compare genotype/phenotype associations in order to understand the pathogenic basis of neoplastic and non-neoplastic diseases linked to mitochondrial dysfunction.

Technological Features

- *Early Cancer* associated mutations detected in 88% of patients.
- *Non-invasive* samples (BAL, Urine, Sputum, NAF) contained the identical mutations as observed in the primary tumor tissue.
- Assay format is readily *transferable to point of care*.

Publications:

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- Jakupciak, J.P., O'Connell, C.D.,. **Standards and Standardization of Molecular Diagnostics.** as Part V: Quality Assurance in Molecular Diagnostic Laboratories, in Molecular Diagnostics for the Clinical Laboratorian, Second Edition, Eds. G. Tsongalis, Humana Press, Inc. Totowan, NJ, 243-246, (2005)

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